

### REMARKS

At the outset, the Applicants wish to thank Patent Examiner Irene Marx for the many courtesies extended to the undersigned attorney during the Personal Interview on April 21, 2004. The substance of this Personal Interview is presented in the Examiner Interview Summary, and in this Amendment.

The Patent Examiner has requested in the Interview Summary that copies of Specification pages 8 to 11, 17, 19, 22 and 23 be provided for clarity, wherein the numeral subscripts and superscripts be darkened for purposes of legibility. Therefore, these corrected pages are now being provided. It is respectfully requested that these corrected pages replace the original and objected to Specification pages 8 to 11, 17, 19, 22 and 23.

The amendments to this patent application are as follows. On pages 14 to 15 of the present Specification, the numbers have been corrected to include a comma, or commas, where necessary. In the present Specification, on pages 12, 13, 19 and 20, each trademark has been revised to be written in all capital letters, and where necessary, the active ingredient for the product is listed, for which product the trademark is used.

Claim 1 has been amended to cancel the phrase "or enantio-

enriched". Claim 1 has been amended to recite "cleaving the dioxolane or oxathiolane ring". Minor revisions have been made to claim 2. Claims 9 and 10 have been amended to cancel the word "cosolvent" and to replace with the word "solvent". Claim 13 has been amended to cancel the phrase "and a solvent".

No new matter has been introduced by this Amendment.

In the Advisory Action dated August 20, 2004, the Patent Examiner stated that the proposed Amendment filed July 8, 2004, raises new issues that would require further consideration and/or search with respect to the extensive spaces added in recitations at the last line of page 8, "C<sub>6</sub>-C<sub>18</sub>-aryl -C<sub>1</sub>-C<sub>18</sub>-alkyl", for example, in the next two lines on page 9 and throughout the proposed claims. These spaces were objected to by the Patent Examiner.

In response to these objections, the "extensive spaces" on pages 8 and 9 have been eliminated. Withdrawal of this objection is respectfully requested.

Also in the Advisory Action dated August 20, 2004, the Patent Examiner stated that no instructions are provided regarding the entry of replacement pages 8-11, 17, 19, and 22-23, and in view of the extent of the replacement pages, a statement

that no new matter is introduced seems appropriate.

In response to these objections, instructions have been provided regarding the entry of replacement pages 8 to 11, 17, 19, and 22 to 23. Also, a statement has been made that no new matter has been introduced by this Amendment.

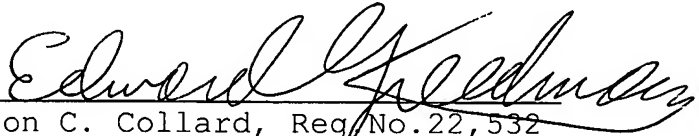
Entry and consideration of this Supplemental Amendment is respectfully requested.

For all these reasons, the Specification, and all the claims, are now in complete compliance with the requirements of 35 U.S.C. 112. Withdrawal of this ground of rejection is respectfully requested. A prompt notification of allowability is respectfully requested.

Respectfully submitted,

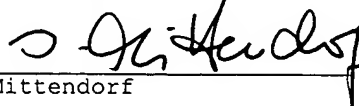
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Enclosures: 1) Copy Spec Pages 8 to 11, 17, 19, 22 and 23

I hereby certify that this correspondence is being deposited with the U.S. Postal Service as first class mail in an envelope addressed to: Commissioner of Patents, P.O. Box 1450, Alexandria, VA 22313-1450 on October 13, 2004.

  
Ingrid Mittendorf

## Equation 5

where X = oxygen or sulfur and

the radicals  $R^1$  and  $R^2$  are different and are selected independently of one another from the group consisting of H, substituted or unsubstituted  $C_6-C_{18}$ -aryl,  $C_3-C_{18}$ -heteroaryl,  $C_1-C_{18}$ -alkyl,  $C_2-C_{18}$ -alkenyl,  $C_2-C_{18}$ -alkynyl,  $C_6-C_{18}$ -aryl- $C_1-C_{18}$ -alkyl,  $C_3-C_{18}$ -heteroaryl- $C_1-C_{18}$ -alkyl,  $C_6-C_{18}$ -aryl- $C_2-C_{18}$ -alkenyl,  $C_3-C_{18}$ -heteroaryl- $C_2-C_{18}$ -alkenyl,  $C_1-C_{18}$ -alkoxy- $C_1-C_{18}$ -alkyl,  $C_1-C_{18}$ -alkoxy- $C_2-C_{18}$ -alkenyl,  $C_6-C_{18}$ -aryloxy- $C_1-C_{18}$ -alkyl,  $C_6-C_{18}$ -aryloxy- $C_2-C_{18}$ -alkenyl,  $C_3-C_8$ -cycloalkyl,  $C_3-C_8$ -cycloalkyl- $C_1-C_{18}$ -alkyl,  $C_3-C_8$ -cycloalkyl- $C_2-C_{18}$ -alkenyl, and  $CR^8R^9-O_n-(CO)_m-R^{10}$  and the radicals  $R^3$  and  $R^4$  are selected independently of one another from the group consisting of substituted or unsubstituted  $C_1-C_{18}$ -aryl,  $C_1-C_{18}$ -heteroaryl,  $C_1-C_{18}$ -alkyl,  $C_2-C_{18}$ -alkenyl,  $C_2-C_{18}$ -alkynyl,  $C_6-C_{18}$ -aryl- $C_1-C_{18}$ -alkyl,  $C_3-C_{18}$ -heteroaryl- $C_1-C_{18}$ -alkyl,  $C_6-C_{18}$ -aryl- $C_2-C_{18}$ -alkenyl,  $C_3-C_{18}$ -heteroaryl- $C_2-C_{18}$ -alkenyl,  $C_1-C_{18}$ -alkoxy- $C_1-C_{18}$ -alkyl,  $C_1-C_{18}$ -alkoxy- $C_2-C_{18}$ -alkenyl,  $C_6-C_{18}$ -aryloxy- $C_1-C_{18}$ -alkyl,  $C_6-C_{18}$ -aryloxy- $C_2-C_{18}$ -alkenyl,  $C_3-C_8$ -cycloalkyl,  $C_3-C_8$ -cycloalkyl- $C_1-C_{18}$ -alkyl, and  $C_3-C_8$ -cycloalkyl- $C_2-C_{18}$ -alkenyl or the radicals  $R^3$  and  $R^4$  form, together with the carbon to which they are bonded, an unsubstituted or substituted or a heteroatom-containing cycloalkylidene and Nu is  $OR^5$ ,  $SR^5$  or

$NR^6R^7$ , where

the radicals  $R^5$  are selected from the group consisting of H, substituted or unsubstituted  $C_1$ - $C_{18}$ -alkyl,  $C_2$ - $C_{18}$ -alkenyl,  $C_2$ - $C_{18}$ -alkynyl,  $C_6$ - $C_{18}$ -aryl- $C_1$ - $C_{18}$ -alkyl,  $C_3$ - $C_{18}$ -heteroaryl- $C_1$ - $C_{18}$ -alkyl,  $C_6$ - $C_{18}$ -aryl- $C_2$ - $C_{18}$ -alkenyl, and  $C_3$ - $C_{18}$ -heteroaryl- $C_2$ - $C_{18}$ -alkenyl, and the radicals  $R^6$  and  $R^7$  are selected

independently of one another from the group consisting of H, substituted or unsubstituted  $C_1$ - $C_{18}$ -alkyl,  $C_2$ - $C_{18}$ -alkenyl,  $C_2$ - $C_{18}$ -alkynyl,  $C_6$ - $C_{18}$ -aryl,  $C_3$ - $C_{18}$ -heteroaryl,  $C_6$ - $C_{18}$ -aryl- $C_1$ - $C_{18}$ -alkyl,  $C_3$ - $C_{18}$ -heteroaryl- $C_1$ - $C_{18}$ -alkyl,  $C_6$ - $C_{18}$ -aryl- $C_2$ - $C_{18}$ -alkenyl, and  $C_3$ - $C_{18}$ -heteroaryl- $C_2$ - $C_{18}$ -alkenyl,

and the radicals  $R^8$  and  $R^9$  are selected independently of one another from the group consisting of substituted or

unsubstituted  $C_6$ - $C_{18}$ -aryl,  $C_3$ - $C_{18}$ -heteroaryl,  $C_1$ - $C_{18}$ -alkyl,  $C_2$ - $C_{18}$ -alkenyl,  $C_2$ - $C_{18}$ -alkynyl,  $C_6$ - $C_{18}$ -aryl- $C_1$ - $C_{18}$ -alkyl,  $C_3$ - $C_{18}$ -heteroaryl- $C_1$ - $C_{18}$ -alkyl,  $C_6$ - $C_{18}$ -aryl- $C_2$ - $C_{18}$ -alkenyl,  $C_3$ - $C_{18}$ -heteroaryl- $C_2$ - $C_{18}$ -alkenyl,  $C_1$ - $C_{18}$ -alkoxy- $C_1$ - $C_{18}$ -alkyl,  $C_1$ - $C_{18}$ -alkoxy- $C_2$ - $C_{18}$ -alkenyl,  $C_6$ - $C_{18}$ -aryloxy- $C_1$ - $C_{18}$ -alkyl,  $C_6$ - $C_{18}$ -aryloxy- $C_2$ - $C_{18}$ -alkenyl,  $C_3$ - $C_8$ -cycloalkyl,  $C_3$ - $C_8$ -cycloalkyl- $C_1$ - $C_{18}$ -alkyl, and  $C_3$ - $C_8$ -cycloalkyl- $C_2$ - $C_{18}$ -alkenyl or the radicals

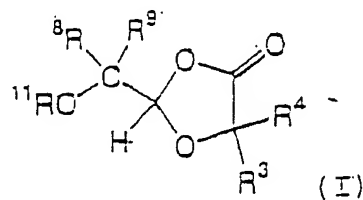
$R^8$  and  $R^9$  form, together with the carbon to which they are bonded, an unsubstituted or substituted or a heteroatom-containing cycloalkylidene, and m and n are, independently of one another, 0 or 1, and the following applies to the radical

$R^{10}$ : if  $m$  is 0 then the radical  $R^{10}$  is selected from the group consisting of substituted or unsubstituted  $C_1$ - $C_{18}$ -alkyl,  $C_2$ - $C_{18}$ -alkenyl or  $C_2$ - $C_{18}$ -alkynyl, substituted or unsubstituted  $C_6$ - $C_{18}$ -aryl,  $C_3$ - $C_{18}$ -heteroaryl, and substituted or unsubstituted silaalkyl or silaaryl, and if  $m$  is 1 then the radical  $R^{10}$  is selected from the group consisting of substituted or unsubstituted aryl, substituted or unsubstituted  $C_1$ - $C_{18}$ -alkyl,  $C_2$ - $C_{18}$ -alkenyl, or  $C_2$ - $C_{18}$ -alkynyl.

Where the radicals are substituted radicals, these are preferably substituted by alkyl, alkenyl, alkynyl, aryl, heteroaryl, hydroxyl, alkoxy, carboxylate, alkoxycarbonyl, amino, nitro or halo radicals.

Where the abovementioned radicals contain a heteroatom, it is preferably O, N or S.

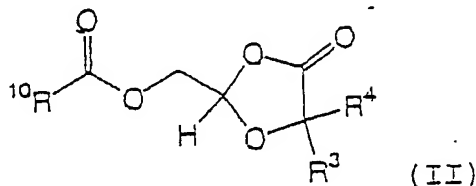
Mixtures of enantiomers of the general formula (I)



where  $R^3$ ,  $R^4$ ,  $R^8$  and  $R^9$  have the meaning mentioned above, and  $R^{11}$  are substituted or unsubstituted, branched or unbranched  $C_1$ -

C<sub>18</sub>-alkyl, C<sub>2</sub>-C<sub>18</sub>-alkenyl or C<sub>2</sub>-C<sub>18</sub>-alkynyl, substituted or unsubstituted aryl, substituted or unsubstituted silaalkyl or silaaryl, or R<sup>11</sup> is COR<sup>11</sup> where R<sup>10</sup> has the meaning mentioned above, are preferably used.

Mixtures of enantiomers of the general formula (II)



where R<sup>3</sup> and R<sup>4</sup> have the meaning mentioned above, and R<sup>10</sup> is selected from the group consisting of substituted or unsubstituted aryl, substituted or unsubstituted C<sub>1</sub>-C<sub>18</sub>-alkyl, C<sub>2</sub>-C<sub>18</sub>-alkenyl and C<sub>2</sub>-C<sub>18</sub>-alkynyl, are particularly preferably used.

The nucleophile NuH is preferably an oxygen-containing nucleophile OR<sup>5</sup>.

The oxygen-containing nucleophile is particularly preferably a lower, unbranched alcohol, (e.g. methanol (R<sup>5</sup> = CH<sub>3</sub> or ethanol (R<sup>5</sup> = CH<sub>2</sub>CH<sub>3</sub>)) or water R<sup>5</sup> = H).

All enzymes able to cleave an ester linkage are in

terminating the pumping.

The uncleaved, pure enantiomer is preferably isolated by removing the byproducts of the reaction and the solvent.

The free carbonyl compound  $R^1COR^2$  resulting from the cleavage of a 1,3-dioxolan-4-one or 1,3-oxathiolan-5-one ring and the acid derivative  $HXCR^3R^4CONu$  can be removed from the reaction solution by simple physical operations. This preferably takes place by distillation.

It is additionally possible for further breakdown products formed on cleavage of other functional groups in the molecule to be removed easily. This preferably takes place by distillation.

It is preferred for the low-boiling compounds to be removed first by distillation. It has been found, surprisingly, that the alcohol ( $R^1 = H$ ,  $R^2 = CH_2OH$ ) which is a byproduct of the racemate resolution of an ester dioxolanone ( $X = O$ ;  $R^1 = H$ ,  $R^2 = CH_2-O-(CO)-R^{10}$ ) can be removed by simple extraction, preferably with water.

The carbonyl compound resulting from the enzymatic




considered in connection with the accompanying examples. It is to be understood, however, that the examples are designed as an illustration only and not as a definition of the limits of the invention.

Example 1: (4-oxo-1,3-dioxolan-2-yl)methyl (+)-(R)-2-methylpropanoate (batch process)

50.0 g (0.27 mol) of racemic (4-oxo-1,3-dioxolan-2-yl)methyl 2-methylpropanoate ( $X = O$ ;  $R^1 = H$ ;  $R^2 = CH_2-O-(CO)-CH(CH_3)_2$ ;  $R^3, R^4 = H$ ) are dissolved in a mixture of 185 ml of MTBE and 185 ml of methanol ( $Nu = OCH_3$  in a 1 l 4-necked flask. 2.6 g of Novozym® 435 are added to this solution, and the mixture is stirred vigorously.

A polarimeter is connected via a bypass system to the 4-necked flask and is used to follow the progress of the reaction through measurement of the optical rotation of the solution. When the desired enantiopurity (reaction followed by chiral GC) is reached, the reaction is terminated by filtering the reaction mixture to remove undissolved enzymes. The reaction mixture is then concentrated in vacuo. The residue is then taken up in 100 ml of MTBE and washed twice

	Substituents in equation 5	Racemate	Product	Selectivity according to Sih*
3	$X = O; R^1 = H; R^2 = -CH_2-C_6H_5$ $R^3, R^4 = H$		(+)-2-Methylphenyl-1,3-dioxolan-4-one	11
4	$X = O; R^1 = H; R^2 = -C_6H_{11}$ $R^3, R^4 = H$		(+)-2-Cyclohexyl-1,3-dioxolan-4-one	65
5	$X = O; R^1 = H; R^2 = -CH(CH_3)_2$ $R^3, R^4 = H$		(+)-2-iso-Propyl-1,3-dioxolan-4-one	14
6	$X = O; R^1 = H; R^2 = -C_7H_{15}$ $R^3, R^4 = H$		(+)-2-Heptyl-1,3-dioxolan-4-one	13
7	$X = S; R^1 = H; R^2 = -C_6H_{11}$ $R^3, R^4 = H$		(+)-2-Cyclohexyl-1,3-oxathiolan-5-one	65

<p>8 X = S; R<sup>1</sup> = H; R<sup>2</sup> = -CH<sub>2</sub>O(CO) - CH(CH<sub>3</sub>)<sub>2</sub> R<sup>3</sup>, R<sup>4</sup> = H</p>		<p>(+) - Isobutyryloxy-methyl-1,3-oxathiolan-5-one</p>	<p>65</p>
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\* Chen, C.-S. et al., J. Am. Chem. Soc. 104, 7294-7299 (1982)